wherein the serotype or serosubtype of each of the first and second *Neisseria meningitidis* species is different, and wherein administering of the first and second preparations elicits an immune response in said mammal, wherein said immune response confers protective immunity against more than one strain of *Neisseria meningitidis* species.

48. **(New)** The method of claim 47, further comprising:

administering to said mammal a third preparation of outer membrane vesicles (OMV), MVs, or both OMVs and MVs from a third *Neisseria meningitidis* species that is a member of a third serotype and of a third serosubtype, in an amount sufficient to elicit an immune response to epitopes present in said third preparation.

49. **(New)** The method of claim 48, wherein the first, second, and third preparations are administered serially.

REMARKS

FORMAL MATTERS:

Claims 1-10 and 12-15, 20-27, and 40-49 are pending after entry of the amendments set forth herein.

Claim 11 is canceled without prejudice.

Claims 16-19 and 28-39 are canceled without prejudice as being drawn to non-elected subject matter.

Claims 1, 5, 7-9, 14, and 21-22 are amended for further clarity and/or to correctly typographical errors.

New claims 40-49 are added. Support for these new claims is found in, for example, original claim 1-8; and specification paragraph [0084].

The specification is amended to properly refer to the trademarks kindly noted by the Examiner.

Applicants note the several claims were previously amended in a Preliminary Amendment mailed January 16, 2002.

No new matter is added.

OVERVIEW OF THE RESPONSE

The present invention is directed to a method for eliciting protective immunity against *Neisseria meningitidis* by administration of preparations of microvesicles (MV), outer membrane vesicles (OMV), or both MV and OMV from *N. meningitidis* as recited in the claims.

Rejections under §112, ¶2

The claims were variously rejected under §112, ¶2. These rejections are addressed herein.

Rejections under §112, ¶1

The claims were also rejected under §112, ¶1 on the grounds that the specification, while enabling for methods of producing neutralizing antibodies, does not provide an enabling disclosure for methods directed to eliciting broad spectrum protective immunity against *Neisseria meningitidis* and diseases caused by *N. meningitidis* species. Applicants have shown that the claimed methods elicit bactericidal antibodies in mice and in guinea pigs, which bactericidal antibodies provide for passive protection against bacterial challenge in an infant rat model. However, the Examiner indicated during the interview that while the data in the specification was extensive, the specification did not provide data using an animal model in which both immunization and challenge occurred.

As discussed during the interview, *N. meningitidis* is unique with respect to immune response sufficient to provide protective immunity. Unlike many other pathogenic organisms, the presence of bactericidal antibodies is an indicator of protective immunity. Protective immunity and bactericidal antibodies go hand-in-hand. This is not to imply that bactericidal antibodies are the only measure of a protective immune response, or are necessarily or absolutely required. However, if bactericidal antibodies *are* in fact present, it is well-accepted that protective immunity is present. The presence of bactericidal antibodies is so well-established as an indicator of protective immunity that a measure of bactericidal antibodies has been a primary basis for licensure of *N. meningitidis* vaccines without the need for an efficacy trial. As discussed in more detail below, this has been true for both conjugate vaccines and outer membrane vesicle (OMV) vaccines.

The specification has shown that the claimed method results in production of bactericidal antibodies, which elicit activity in both *in vitro* assays as well as in an *in vivo* animal model. Applicants respectfully submit that the specification is fully enabling and this rejection can be withdrawn. Applicants' position in this regard is set forth in more detail below.

INTERVIEW SUMMARY

Applicants wish to express their gratitude to Examiner Zeman for the telephonic interview on May 13, 2004. The undersigned and the co-inventors Dan Granoff and Gregg Moe participated.

The rejections of the claims under §112, ¶2 and §112, ¶1 were discussed. Specifically, the Examiner agreed that the amendments and remarks as set out herein would serve to obviate the rejections under §112, ¶2. In addition, the Examiner indicated he would consider favorable applicants' arguments regarding the enablement rejection under §112, ¶1 in view of the assertions regarding the role of serum bactericidal antibodies in providing protective immunity against *Neisseria meningitidis*, as discussed in detail below.

OBJECTIONS TO THE SPECIFICATION

Use of trademarks

The objection to the specification as it relates to the use of trademarks is addressed by amendment, and may be withdrawn.

ATCC deposit numbers

With respect to the objection to the specification relating to incomplete ATCC deposit information, applicants note that paragraph [00207] on page 60 of the specification was amended to include the deposition information in Preliminary Amendment, filed August 21, 2001.

Page 51 does not refer to any specific deposit information that is missing. The prior amendment to page 61 in the Preliminary Amendment should be sufficient to address this informality.

Withdrawal of the objections to the specification is respectfully requested.

OBJECTIONS TO THE CLAIMS

The objection to claim 11 is rendered moot by cancellation of this claim. Withdrawal of this objection is respectfully requested.

REJECTIONS UNDER §112, ¶1

Claims 1-15 and 20-27 were rejected on the grounds that, while enabled for methods of producing neutralizing antibodies, the claims methods are not enabled for eliciting broad spectrum protective immunity against *Neisseria meningitidis* and diseases caused by *N. meningitidis* species.

The Office Action bases this rejection on the assertion that the specification does not set forth that the claimed invention provides any sort of protective immunity in any model system that can be extrapolated to humans or other mammals. (Office Action, page 3, bottom) The Office Action states that

> Applicant describes methods of producing antibodies (i.e. antisera) that is [sic] bactericidal *in vitro* but fails to demonstrate that the claimed method provides protective immunity (broad spectrum or otherwise) in any animal system other than ruminants. Moreover, the specification is silent on what 'diseases' can be prevented by the claimed methods." (Office Action, text bridging pages 3-4)

This rejection is respectfully traversed.

First, with respect to the aspect of the rejection relating to the "diseases" that can be prevented by the claimed methods, applicants respectfully submit that the amendments to the claims serve to further clarify the claimed invention, rendering this rejection moot.

The remaining aspects of the rejection are addressed below.

The specification provides ample evidence to support the assertion that the claimed methods provide to protective immunity against multiple strains, including serotype and serosubtypes, of N. meningitidis

As stated in the specification at paragraph [00178], finding that a vaccine produces bactericidal antibodies against *Neisseria meningitidis* is accepted in the field as an indicator of the vaccine's protective effect.[1] This is true of both conjugate-based[2], outer membrane protein-based and conjugate-

[1] See, e.g., Goldschneider et al., Human immunity of the meningococcus, I. The role of humoral antibodies, 1969, *J. Exp. Med.* 129:1307 (Exhibit 1).
[2] Borrow et al., Serological basis for use of meningococcal serogroup C conjugate vaccines in the united kingdom: reevaluation of correlates of protection, 2001 Infect Immun. 69:1568 (Exhibit 2).

based,[3] and outer membrane vesicle(OMV)-based[4] vaccines. As also stated in the specification at paragraph [00184], the infant rat model is a model of *N. meningitidis* infection.

The specification provides data showing that the claimed invention provides for production of anti-*N. meningitidis* antibodies that are bactericidal (specification paragraphs [00178] – [00183]) and that provide for passive protection against infection in the infant rat model (specification paragraphs [00184] – [00187]).

While applicants believe the statements above should suffice to overcome this rejection, for the Examiner convenience, the discussion below provides more details in support of applicants' position. Applicants provide 1) a review of the literature supporting the assertion that production of bactericidal antibodies is evidence suggesting that a protective immune response has been elicited; and 2) a discussion of the results in animal models as presented in the specification.

Bactericidal activity of antibodies against Neisseria meningitidis is an art-accepted indicator of predictor of protection against invasive meningococcal disease

The bactericidal assay measures the interaction of antibody and complement at the bacterial surface, which results in bacterial death. Several lines of evidence, summarized below, prove that the presence of serum bactericidal activity is a reliable predictor of protection against invasive meningococcal disease (disease defined as invasion of the bloodstream by the bacteria [bacteremia] and/or invasion of the membranes covering the brain (meningitis).

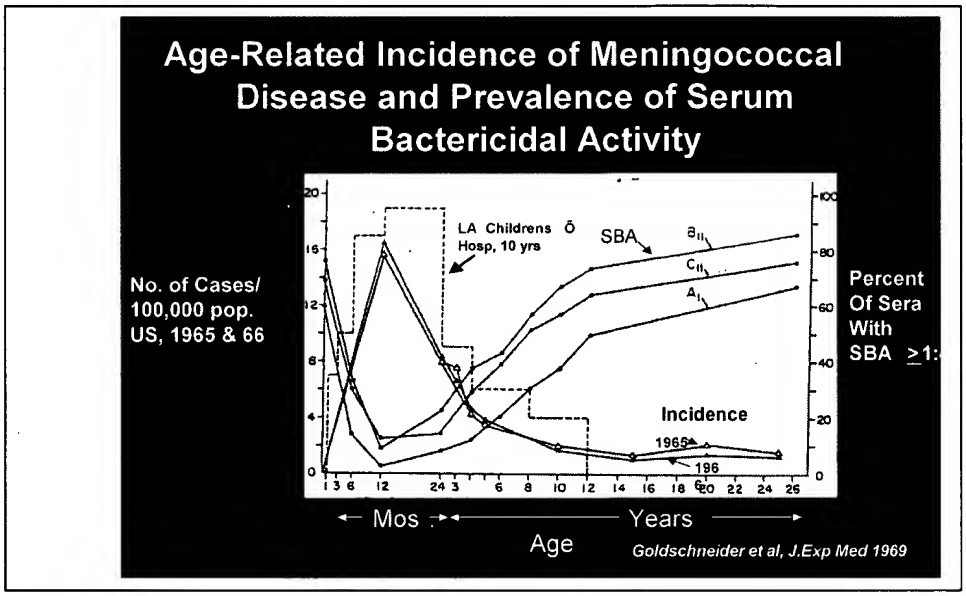
1. Age-incidence of meningococcal disease is inversely related to the prevalence of meningococcal disease

Most newborns have serum bactericidal antibodies that are acquired transplacentally from their mothers and persist in the infant for a few months (see graph below).[5] Thereafter, natural acquisition of serum bactericidal antibodies to *N. meningitidis* is inversely related to age. Low levels of bactericidal antibodies are present below 2 years, which corresponds to the age group at greatest risk of acquiring

---

[3] Milagres et al., Immune response of Brazilian children to a *Neisseria meningitidis* serogroup B outer membrane protein vaccine: comparison with efficacy. Infect Immun 1994;62:4419-24 (Exhibit 3)
[4] Holst et al., Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. Vaccine 2003, 21:734-737 (Exhibit 4).
[5] Goldschneider et al., *supra* (Exhibit 1)

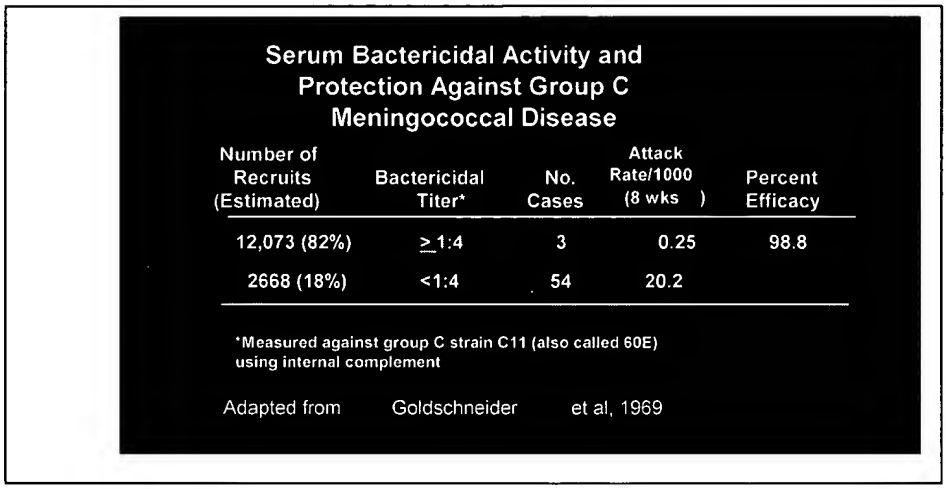
meningococcal disease. Between 2 and 12 years of age there is a progressive increase in the prevalence of serum bactericidal antibody, which coincides with a progressive decrease in the incidence of meningococcal disease in the population.



2. Persons with naturally-acquired serum bactericidal antibody are protected against developing meningococcal disease.

In their seminal study, Goldschneider et al demonstrated the importance of naturally-acquired serum bactericidal antibodies in protection against group C meningococcal disease during an epidemic among military recruits in the 1960s.[6] Group C bactericidal antibodies were present in baseline sera of approximately 82 percent of the recruits. Those with detectable serum bactericidal antibody frequently became carriers of the epidemic strain but did not develop meningococcal disease while virtually all cases of disease occurred in the 18 percent of individuals whose baseline sera lacked bactericidal activity (titers <1:4 measured with human complement). Recruits who lacked serum bactericidal antibody and developed group C carriage had meningococcal disease attack rates as high as 38.5 percent. The "efficacy" of a bactericidal titer of 1:4 or greater was >98%.

[6] Goldschneider et al., *supra* (Exhibit 1).



Serum Bactericidal Activity and Protection Against Group C Meningococcal Disease

Number of Recruits (Estimated)	Bactericidal Titer*	No. Cases	Attack Rate/1000 (8 wks)	Percent Efficacy
12,073 (82%)	≥1:4	3	0.25	98.8
2668 (18%)	<1:4	54	20.2	

*Measured against group C strain C11 (also called 60E) using internal complement

Adapted from Goldschneider et al, 1969

3. Serum bactericidal activity is accepted in the art as a correlate with vaccine efficacy against Neisseria meningitidis

As a result of the seminal Goldschneider data, serum bactericidal antibody (SBA) titers are a principal basis for licensure of meningococcal vaccines.[7,8,9,10]

Notably, the World Health Organization,[11] and regulatory agencies in Europe and the U.S., require a showing of serum bactericidal antibody responses as an indicator of vaccine efficacy for licensure of new meningococcal vaccines. For licensure of the tetravalent meningococcal polysaccharide vaccines in the U.S, the efficacy of the group Y and W135 components was inferred based on 4-fold or greater bactericidal antibody responses.[12] In the United Kingdom, the efficacy data supporting licensure of the new group C meningococcal polysaccharide-protein conjugate vaccines were based on serologic responses, with bactericidal titers being the most important single criterion.[13] These vaccines were subsequently licensed in Europe, Canada and elsewhere based on these data.

---

[7] Borrow et al., *supra* (Exhibit 2).
[8] Balmer, et al., Serologic correlates of protection for evaluating the response to meningococcal vaccines. Expert Rev Vaccines 2004;3:89-99 (Exhibit 5).
[9] Milagres et al., *supra* (Exhibit 3)
[10] Holst et al., *supra* (Exhibit 4)
[11] World Health Organization. Requirements for meningococcal polysaccharide vaccine (requirements for biological substances no. 23). WHO Tech Rep Ser 1976;594:1-86, see particularly pages 19 and 72 – 73 (Exhibit 6)
[12] 50 Fed. Reg. 162, Guidelines for Production of Meningococcal Polysaccharide Vaccines Docket No. 84D-0263, Notice of Availability Published August 21, 1985 (Exhibit 7).
[13] Borrow et al., *supra* (Exhibit 2)

4. The application provides evidence of production of bactericidal antibodies in mice and in guinea pigs following vaccination according to the claimed methods

The specification provides data showing that the claimed invention provides for production of anti-*N. meningitidis* antibodies that are bactericidal not only against strains of the same serotype or serosubtype as the strains used to generate the vesicles used in vaccination, but also against strains that were of a different serotype or serosubtype (specification paragraphs [00178] – [00183]). The production of such bactericidal antibodies was shown in both mice and in guinea pigs. Immune responses in mice in guinea pigs can differ from those in humans; however, the ordinarily skilled artisan would find this data in two different animal models sufficient evidence to merit the inordinate expense involved in trials in a primate model or in humans.

In short, this data provides an indication that bactericidal antibodies can indeed be produced according to the claimed method. The mice and guinea pigs developed high serum titers of bactericidal antibody, which in humans is the accepted correlate of protection against meningococcal disease.

Passive protective activity in the infant rat model.

The inventors described in the application an infant rat meningococcal bacteremia model, which can be used for measuring antibody protective activity against group B or C strains.[14],[15] This model permits investigation of the protective activity of antibodies in a setting where the organism is rapidly replicating *in vivo*.

The specification at paragraphs [00-184] – [00187] and in Figure 10 provides direct data proving that the antibodies elicited in mice by the claimed vaccination method passively confer protection against meningococcal bacteremia in the infant rat model. Figure 11 shows similar data showing that antibodies elicited in guinea pigs by the claimed method also provide for protecting against meningococcal bacteremia in the infant rat model. Thus, applicants have shown, in two different animal species, that the claimed vaccination method elicited antibodies that confer passive protection against meningococcal bacteremia in a bacteremia model. Thus, the bactericidal effect of the serum antibodies

[14] Moe et al., Differences in surface expression of NspA among Neisseria meningitidis group B strains. Infect Immun 1999 67:5664-75 (Exhibit 8).
[15] Harris et al., Age-related disparity in functional activities of human group C serum anticapsular antibodies elicited by meningococcal polysaccharide vaccine. Infect Immun 2003;71:275-86 (Exhibit 9).

produced by the method are not only effective in an in vitro assay, but are also effective in vivo in an animal model of bacteremia.

Conclusion

In view of the ample data in the application relating to production of bactericidal antibodies, and further in view of the additional data from the infant rat model experiments, applicants respectfully submit that the specification provides an enabling disclosure as required by §112, ¶1.

Withdrawal of this rejection of the claims is respectfully requested.

REJECTIONS UNDER §112, ¶2

Claims 1-8 and 20-27 were variously rejected under §112, ¶2. These rejections are specified and addressed below:

Claim 1

Claim 1 was rejected for recitation of "third species" and "third preparation". This rejection is rendered moot by amendment.

Claims 1 and 14, and claims 7 and 9

Claims 1 and 14 were rejected for recitation of "a disease caused by more than one strain of *Neisseria meningitidis* species". Claims 1, 14, 7 and 19 – as well as claim 8 – are amended for clarification to further clarify the invention.

Withdrawal of this rejection is respectfully requested.

Claim 21

Claim 21 was rejected for recitation of "excipients" without antecedent basis. This rejection is rendered moot by amendment, and may be withdrawn.

Claim 22

Claim 22 was rejected for recitation of "the adjuvant" without antecedent basis, and for recitation of improper Markush language. This rejection is rendered moot by amendment, and may be withdrawn.

Withdrawal of the various rejections of the claims under §112, ¶2 is respectfully requested.

INFORMATION DISCLOSURE STATEMENT:

The Applicants note that an Information Disclosure Statement (IDS), including an SB/08A form, was submitted in this application on April 22, 2002. The Applicants respectfully request that the Examiner initial and return this SB/08A form, thereby indicating that the references cited in the IDS have been reviewed and made of record. For the Examiners convenience, a copy of this form is enclosed herewith.

Applicants also submit a further IDS herewith, including an SB/08A form, along with copies of the references cited therein. Applicants respectfully request that the Examiner initial and return this SB/08A form, thereby indicating that the references cited in the IDS have been reviewed and made of record.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CHOR-001.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 21, 2004

By: _____
Carol L. Francis
Registration No. 36,513

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Enclosures: Exhibits 1-9

F:\DOCUMENT\Chor\001\rsp oa 03-22-04 CHOR-001.doc